APPENDIX VI

PHARMACOKINETICS OF NICOTINE AND COTININE

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PHARMACOKINETICS OF NICOTINE AND COTININE

Bioavailability of nicotine inhalation by smoking under steady state conditions

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INTRODUCTION

Cigarettes, cigars and pipes are devices by which nicotine present in the tabacco can be taken up by the body as a result of smoking. Different types or brands of cigarettes may produce different amounts of nicotine in the smoke. The amount of nicotine in the smoke is being determined by standard procedures with smoking machines (FTC method). As a consequence different amounts of smoke are offered to the upper respiratory tract and the lungs, leading to different quantities of nicotine taken up by the body.

Information on actual uptake can be gained by measuring a) the nicotine concentration in the blood, in the urine or other tissue fluids, b) the concentration of a metabolite of nicotine as, e.g. cotinine, or c) the pharmacological effects.

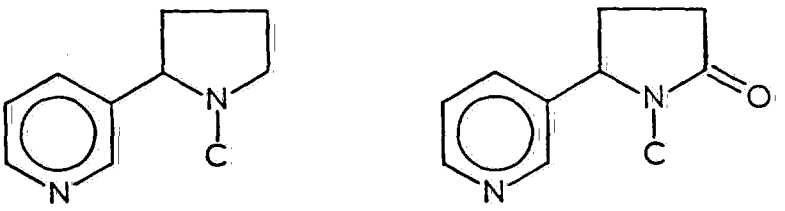

FIG 1. Nicotine and Cotinine Structures

In order to derive the intake of nicotine from the nicotine concentration or metabolite concentration in the blood, knowledge about the disposition and biotransformation of nicotine in the individual subject should be acquired. That is, pharmacokinetic and biopharmaceutic aspects of nicotine and cigarettes should be elaborated.

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PHARMACOKINETICS OF NICOTINE INTAKE: BIOAVAILABILITY

It is possible to study the intake of nicotine or of drugs in general from the output (plasma nicotine, metabolite concentration, etc) if the so-called body transport function of the drug is known. Such studies require large amounts of data, both following i.v. injection and inhalation of nicotine from smoke and are therefore practically not feasible.

It is, however, possible to design the experiments in such a way that a limited number of data per individual are sufficient to answer the relevant questions. These questions are: a) the amount of nicotine taken up by the body, b) the rate at which it occurs and c) eventually the profile of the input function of nicotine.

The study of nicotine intake concentrates on the amount that is taken up (the absolute bioavailability) or in case of brand comparison on the relative amount or uptake ratios (relative bioavailability). The study of the intake of different brands of cigarettes compares to the study of the particular drug in the same dose in various dosage forms as capsules and tablets or different types of tablets.

Since nicotine is rapidly and also to a considerable amount converted into cotinine this metabolite is a candidate for bioavailability measurements (see Figure 1).

PHARMACOKINETIC SYSTEMS DYNAMICS OF NICOTINE

The kinetics of a substance as nicotine in the human body is determined by the physicochemical properties of nicotine and the properties of the various organs and tissues of the body.

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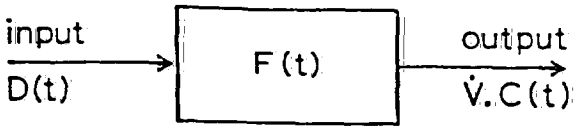

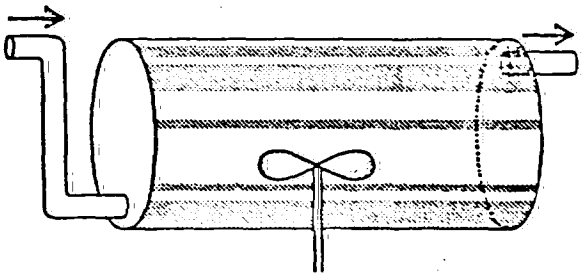

FIG. 2

TABLE 1

SUBSYSTEM: TRANSFER FUNCTION WITH EXTRACTION

$C(t) = \frac{D.(t)}{\dot{V}} * F(t)$ or $C(s) = \frac{D(s)}{\dot{V}} . F(s)$
pulse input (inj.) : $C(t) = \frac{D}{\dot{V}} . F(t)$
step input (infusion): $C(t) = \frac{\dot{D}}{\dot{V}} . \int_0^t F(\lambda)\, d\lambda$
any input : $C(t) = \frac{1}{\dot{V}} . \int_0^t D(t-\lambda).F(\lambda)\, d\lambda$
areas : $AC = \frac{AD}{\dot{V}} . AF \rightarrow AUC = \frac{(1-E)}{\dot{V}} .$ dose
mean times: $TC = TD + TF$ or $MTT = TF$
symbols: $AF = \int_0^\infty F(t)dt$ and $TF = \int_0^\infty t.F(t)dt/AF$

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Subsystems

A tissue or organ may be regarded as a subsystem that receives a drug on the arterial side. Each molecule has a probability to remain in the subsystem for some time, so that a frequency distribution of transit times fully characterizes the tissue. See Figure 2a. Such a tissue may be analogous to a flow vessel (Figure 2b). Then the frequency distribution of transit times would be a single exponential function.

In general, the mean transit time (MTT), the flow of blood through the tissue and its volume are important tissue parameters. They can be obtained by determining the statistical moments of the subsystem transport function. See Table 1.

The intact system

The various subsystems are arranged in series and parallel to each other. The parallel subsystems can be grouped together such that one obtains a positive feedback control system with extraction (see Figure 3). The overall system equation can at once be written down (see Table 2).

The input function, $D_L(t)$, describes the amount of nicotine in the smoke offered to the mouth, upper respiratory tract and the lungs. It will depend on smoking behaviour, the type of cigarette and the type of filter used.

The transport function, $H_L(t)$, from mouth to upper respiratory tract (fraction f_B) and from the bronchioli and alveoli (fraction f_A), describes transport from application site to the aorta. $H_L(t)$ strongly depends on smoking behaviour as depth of inhalation, puff frequency, puff duration etc. This implies that only a fraction (f_L) of the amount of nicotine in the smoke may enter the body.

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INHALATION OF NICOTINE: SAMPLING OF NICOTINE

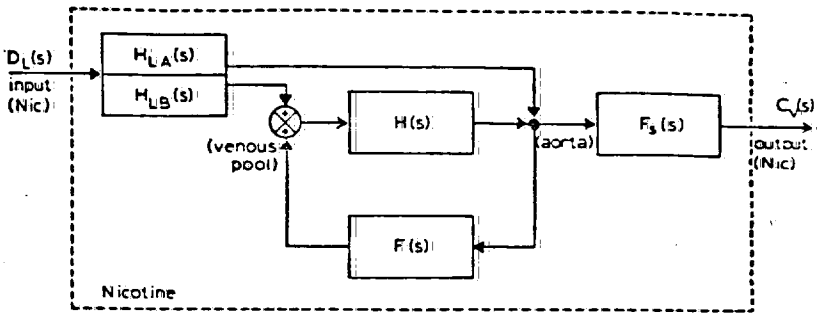

FIG. 3

TABLE 2 NICOTINE INHALATION KINETICS

Input : nicotine from smoke in mouth and respiratory tract

Output: nicotine concentration in venous blood

System equations:

$$C_V(s) = D_L(s) \cdot \frac{\{f_A.H_{LA}(s) + f_B.H_{LB}(s)\ H(s)\}}{\dot{V}_B} \cdot \frac{F_s(s)}{1-F(s).H(s)}$$

or

$$C_V(s) = D_L(s) \cdot H_L(s) \cdot \psi(s)/\dot{V}_{el} \quad \text{and} \quad C_V(t) = D_L(t) * H_L(t) * \psi(t)/\dot{V}_{el}$$

After a single dose ($D_L(t)$ = dose)

area : $AUC_V = \text{dose}.f_L/E.\dot{V}_B = \text{dose}.f_L/\dot{V}_{el}$

mean times: $MRT = TD_L + TH_L + MTT \cdot N_{rc} + TF_s$

During multiple dosing ($D_L(t) = \dot{D}_L$)

steady state: $\bar{C}_{V(pl)} = \dot{D}_L.f_L/\dot{V}_{el}$

$\psi(s)$ is the overall body transfer function for nicotine from aorta to sampling site.

$\psi(t)$ is the corresponding transport function in the real time domain, where * is the symbol of convolution

$H_L(s)$ is the overall transfer function from input site to aorta, where f_A is the fraction taken up in the alveoli and f_B is the fraction via mouth and the bronchi

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TABLE 3

KINETIC SYSTEMS PARAMETERS OF NICOTINE AND COTININE IN MAN

drug	MRT (h)	clearance (l/h)	volume of distribution (l)	Extr. (%)	MIT (min)	N_{rc}
nicotine	2	60	120	20	24	4
cotinine	30	3	90	1	18	100

Nicotine follows input variation

Cotinine averages input variation

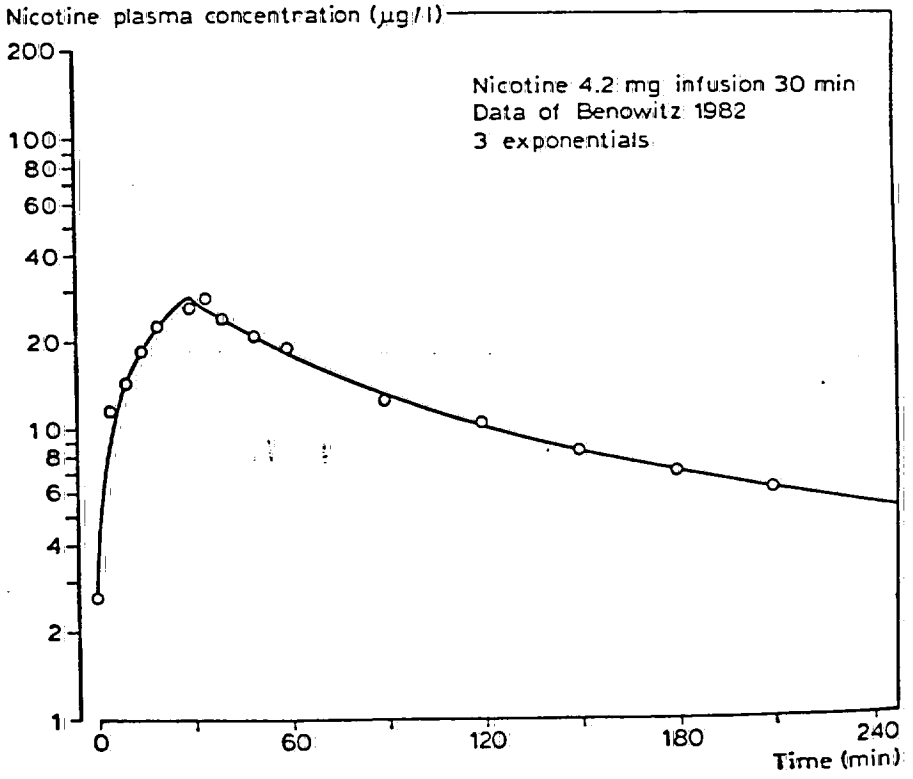

Fig 4

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The function $F_s(t)$ gives the transport from aorta to sampling site (e.g. an arm vene). The function H(t) is the transport function from venous pool to aorta and the function F(t) is the transport function of all tissues of the body, except the heart-lung system. Since liver and kidney are included, extraction takes place here. The molecules that pass F(t) intact may again pass the system (recirculation) (van Rossum et al., 1982).

The relevant kinetic systems parameters: body MTT, extraction E, cardiac output $\dot{V}_B$, clearance $\dot{V}_{el}$ and body mean residence time MRT, with their interrelations are given in Table 2, again using statistical moments.

Total body transport function of nicotine

From plasma nicotine concentration curves following a known input of nicotine the total body transfer function of nicotine can be calculated. We have used i.v. nicotine studies by Benowitz et al. (1982) and Rosenberg et al. (1980) to calculate the body transport function $\psi(t)$ of nicotine in man (Figure 4).

The kinetic systems parameters of nicotine are given in Table 3. The average nicotine takes about 25 min for a single pass through the body. The extraction is about 20%, so that the average number of recirculations is 4 and therefore the mean residence time of nicotine is about 2 hrs. The clearance is about 60 l/h. As a consequence the dynamics of nicotine is fast, which implies that, according to control theory, the output (nicotine plasma concentration) follows the input. The bioavailability (here f_L) can be obtained from the area under the plasma concentration curve following a single dose or smoking a single cigarette, provided that the AUC of a known input has been determined. One does then, however, need to estimate the entire plasma nicotine curve which requires at least 10 data points per individual subject.

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Steady state conditions

During a continuous intake of nicotine as occurs in very regular smoking after some time a steady state condition is reached. Then the average steady state concentration ($C_{V(pl)}$) directly relates to the intake (in mg/h or mg/day), the bioavailability f_L and the clearance $\dot{V}_{el}$ (see Table 2).

The dose depends on the type and brand of cigarette and the way the cigarette is smoked. The bioavailability f_L depends on the smoking behaviour (inhalation etc.) and the clearance merely on the individual (age, weight, etc.).

By comparing brands one should use cigarettes of the same class, since if a smoker is used to high tar cigarettes and switches over to low tar cigarettes, he may increase inhalation depth (behavioural adaptation).

NICOTINE LEVEL AS A MARKER OF NICOTINE INTAKE

From studies by Rosenberg et al. (1980), Benowitz et al. (1982), Russell and Feyerabend (1979, 1980, 1981) the body transfer function of nicotine can be calculated. See Figure 4. As pointed out, the dynamics of nicotine is fast, as its clearance is in the order of 60 l/h and its mean residence time is in the order of 2 hrs. Consequently, the nicotine level follows input variation as predicted by systems control theory. See Figure 5. In this figure 24 cigarettes of 0.2 mg nicotine are very regularly smoked during the day time, every 0.5 h one cigarette during 6 minutes (Fig. 5a). The nicotine transport function as calculated from Fig. 4 is used in Figure 5b. The result of 5a,b is the plasma curve of Figure 5c. Nicotine rapidly acquires a steady state with fluctuations around an average value. The result of five days of very regular smoking is given in Figure 7. It is evident that during the night practically all the nicotine is cleared from the body. Nicotine output (here the concentration) follows the input. Obviously, the variations in the steady

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One day of regular smoking

24 cig/day, one every 1/2 h

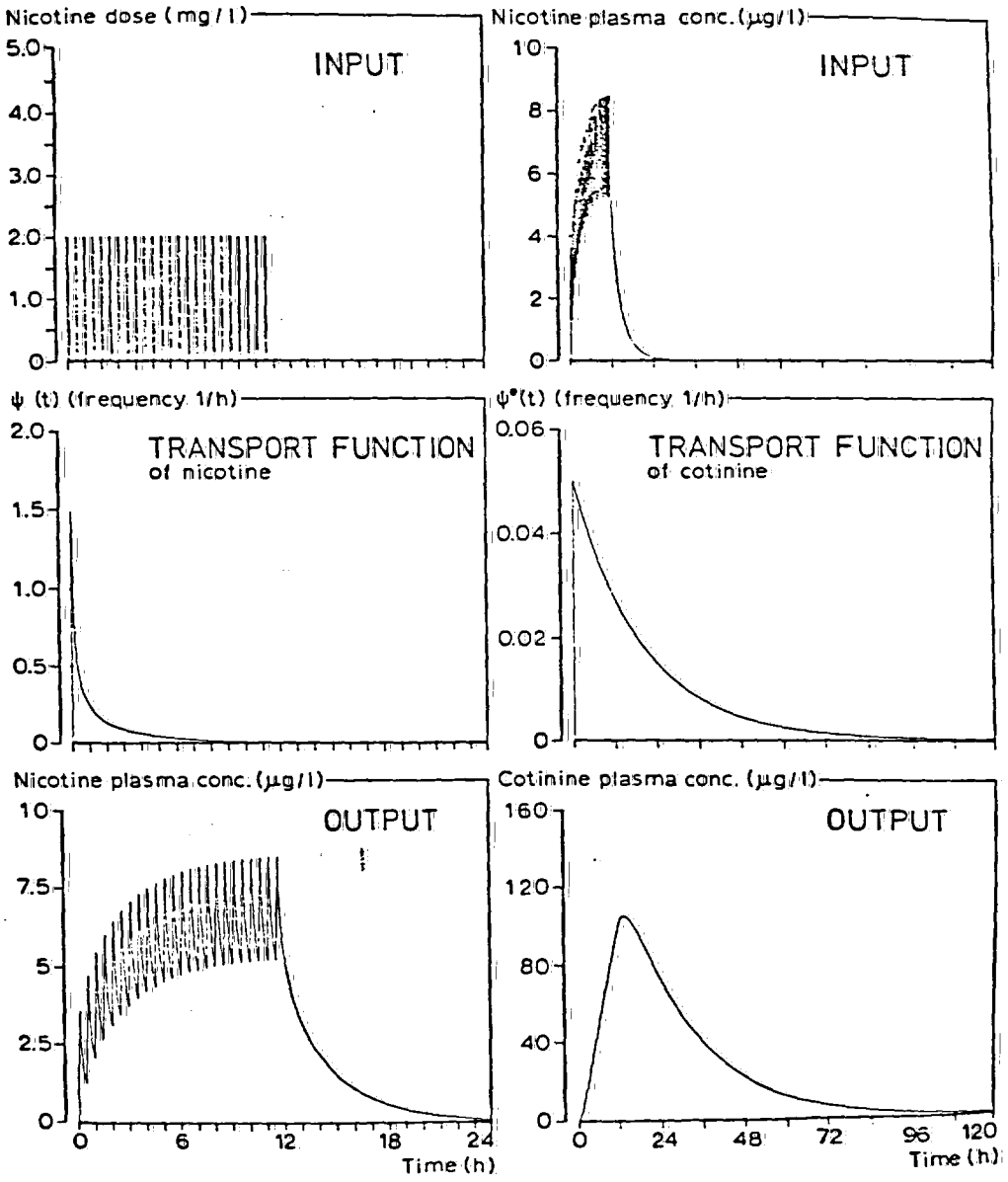

FIG. 5

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state will vary much more when the input varies, as is the case in normal smoking. See Figure 8.

Nicotine can be used as a marker of nicotine input if sufficient blood samples are taken (minimum of 4 in 0.5 h) and the subject smokes regularly. For a drug with a slower dynamics fewer blood samples would suffice.

KINETIC SYSTEMS DYNAMICS OF COTININE

A major metabolite of nicotine is cotinine. The dynamics of cotinine is much slower as its clearance is in the order of 2 l/h and its MRT is in the order of 20 hrs.

The kinetics of cotinine is also according to a positive feedback control system (see Figure 6), but now the extraction is much less and therefore the number of recirculations is much greater. In case of intake of nicotine by smoking the nicotine in the blood is in fact the input for the cotinine. So, the total body transfer function for intake of nicotine and sampling of cotinine includes the transport functions of both drugs in succession. See Table 4.

The kinetic systems parameters of cotinine are given in Table 3. Although the overall transfer function from nicotine input in the respiratory tract to sampling of cotinine in the venous blood is very complex, the steady state level of cotinine again directly relates to the average intake of nicotine, D_L, the fraction of nicotine taken up, f_L, the fraction of nicotine eventually converted into cotinine, f_M^*, and the clearance of cotinine, $\dot{V}_{el}^*$. See Table 4.

Since the clearance of cotinine is much smaller than the clearance of nicotine the steady state level is higher, provided that f_M^* is not very small.

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INHALATION OF NICOTINE: SAMPLING OF COTININE

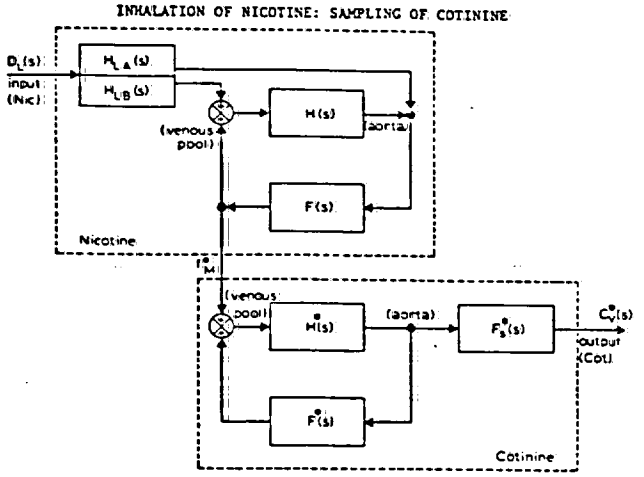

FIG. 6

TABLE 4 NICOTINE, COTININE INHALATION KINETICS

Input : nicotine from smoke in respiratory tract

Output: cotinine concentration in venous blood

System equations:

$$C_V^*(s) = D_L(s)\,\frac{H_L(s)}{\dot{V}_B}\cdot\frac{1}{1-F(s).H(s)}\cdot F(s).f_M^*\cdot\frac{F_s^*(s)}{1-F^*(s).H_s^*}$$

or

$$C_V^*(s) = D_L(s).H_L(s).\psi^*(s)/\dot{V}_{el}^* \quad \text{and} \quad C_V(t) = D_L(t)\circ H_L(t)\circ\psi^*(t)/\dot{V}_{el}^*$$

After single dose ($D_L(t) = D_L$ mg)

area : $AUC_V^* = dose.f_L.f_M^*/E.\dot{V}_B = dose.f_L.f_M^*/\dot{V}_{el}^*$

mean times: $MRT^* = TD_L + TH_L + MIT \cdot N_{rc} + TF + MIT^* \cdot N_{rc}^* + TF_s^*$

During multiple dosing ($D_L(t) = \dot{D}_L$ mg/h)

in steady state:

$$\bar{C}_{V(pl)} = \dot{D}_L \cdot f_L \cdot f_M^*/\dot{V}_{el}^*$$

$\psi^*(s)$ is the overall transfer function of nicotine in the aorta to cotinine in the sampling site

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COTININE AS A MARKER OF NICOTINE INTAKE

The slower dynamics of cotinine also has important consequences for the stability of the steady state. In accordance with control theory the cotinine level is not sensitive to input variation, but on the contrary it averages the input.

In Figure 5 the intake of nicotine (a), the level of nicotine (c, d) and the level of cotinine (f) is given for a typical subject, that smokes very regularly 24 cigarettes per day. In contrast to nicotine, the next morning considerable levels of cotinine are still present.

The calculations for five days very regular smoking clearly show the steady state level of cotinine with peaks at the end of the day. See Figure 7. The calculations for normal smoking in Figure 8 show that cotinine is not sensitive to input variation.

CONCLUSIONS

In spite of the complex dynamics of nicotine and its metabolite cotinine, under steady state conditions the nicotine and cotinine level is directly proportional to the nicotine in the smoke of the cigarette in the same individual adopting a similar smoking behaviour. See Table 5. Under normal smoking conditions the input of nicotine varies, as e.g. the interval between cigarettes smoked is not constant.

The nicotine level follows input variation whereas the cotinine averages input variation. Cotinine is therefore a better marker of daily nicotine input than nicotine, provided that studies are done in the same individuals and under steady state conditions.

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TABLE 5

STEADY STATE CONCENTRATIONS DURING CONTINUOUS NICOTINE INTAKE BY SMOKING

$$\text{Nicotine: } C_{pl} = \frac{\dot{D}_L \cdot f_L}{\dot{V}_{el}} \qquad \text{Cotinine: } C^*_{pl} = \frac{\dot{D}_L \cdot f_L \cdot f^*_M}{\dot{V}^*_{el}}$$

$\dot{D}_L$ = the dose of nicotine in the smoke (mg/h; dependent on type of cigarette)

f_L = the fraction of the nicotine absorbed (dependent on smoking behavior)

$\dot{V}_{el}$ = clearance of nicotine (dependent on the subject)

f^*_M = the fraction of nicotine converted into cotinine (subject-dependent)

$\dot{V}^*_{el}$ = clearance of cotinine (subject-dependent)

By smoking different brands of cigarettes of the same class by the same subject the steady state level of cotinine directly reflects the amount of nicotine in the smoke.

For the same individual ($\dot{V}_{el}$, V^*_{el}, f^*_m constant) with a a similar smoking behavior (f_2 constant) it holds that during steady state:

$$\frac{\textit{cotinine level on brand A}}{\textit{cotinine level on brand B}} = \frac{\dot{D}_L \textit{ brand A}}{\dot{D}_L \textit{ brand B}}$$

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Five days of regular smoking

(24 cig. per day)

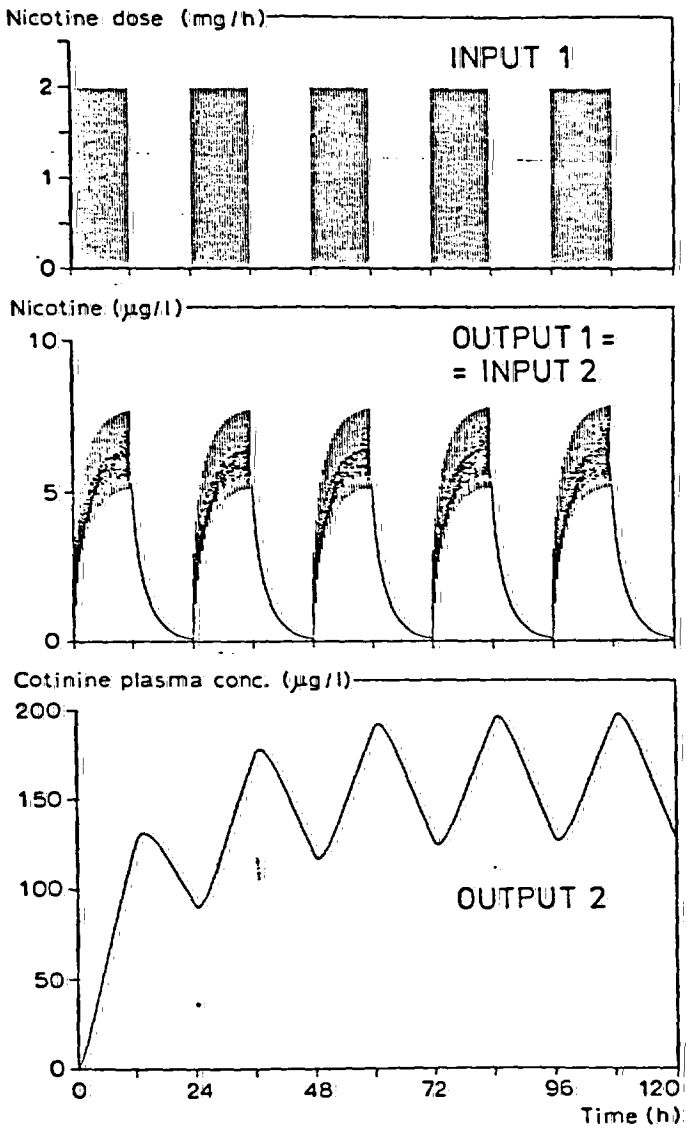

FIG. 7

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Five days of normal smoking

(24 cig. per day)

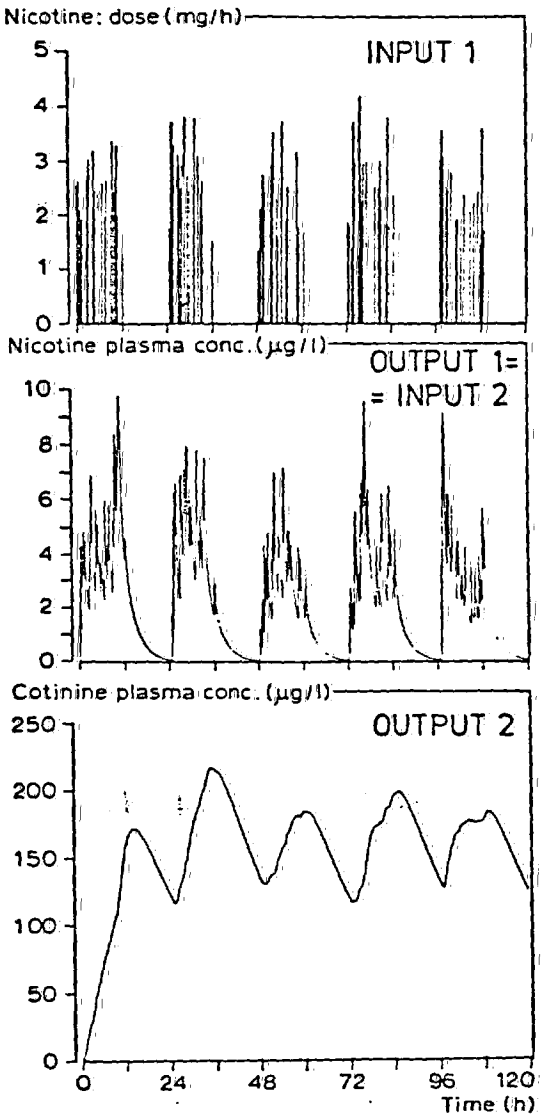

FIG. 8

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